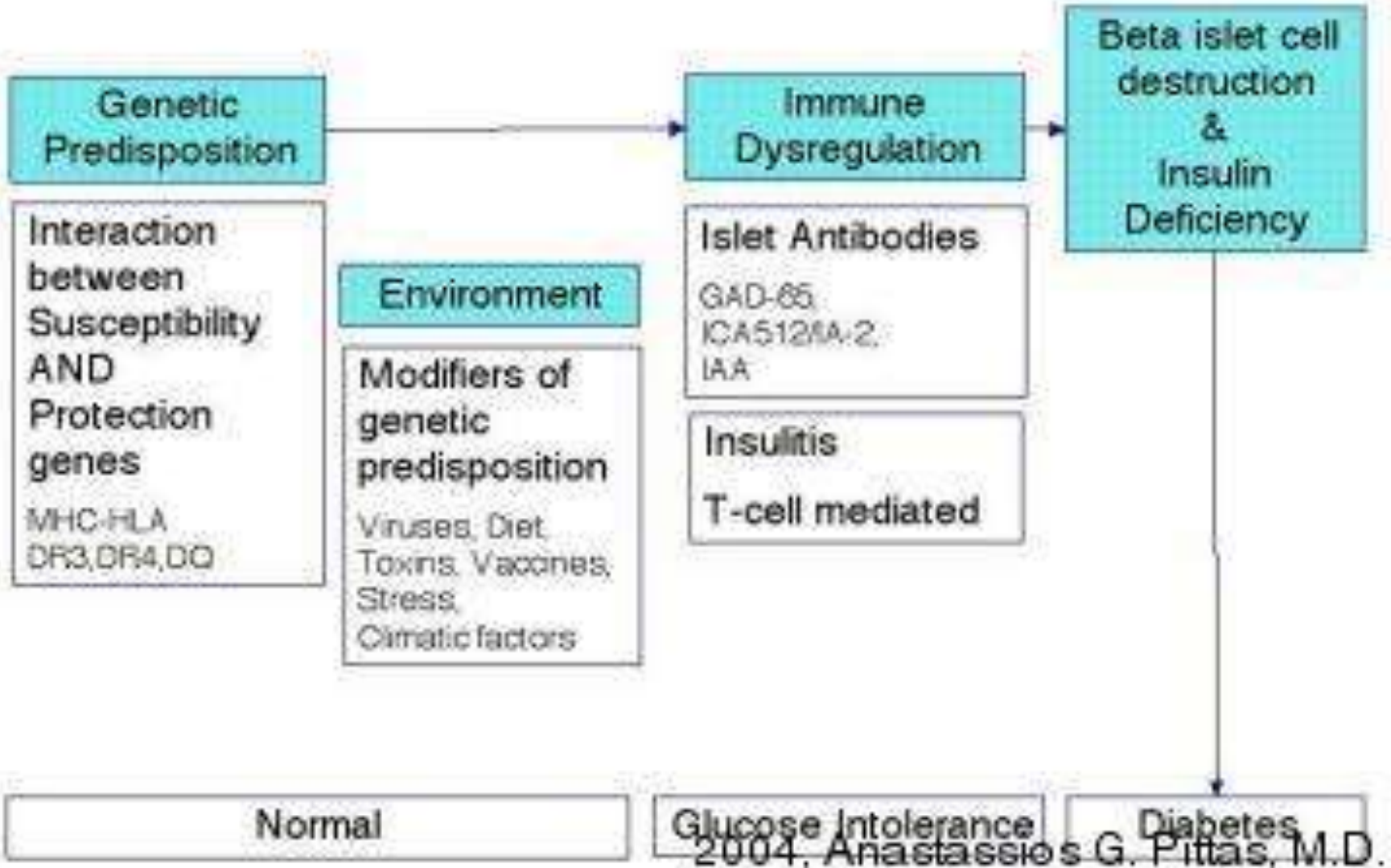
Immunotherapy

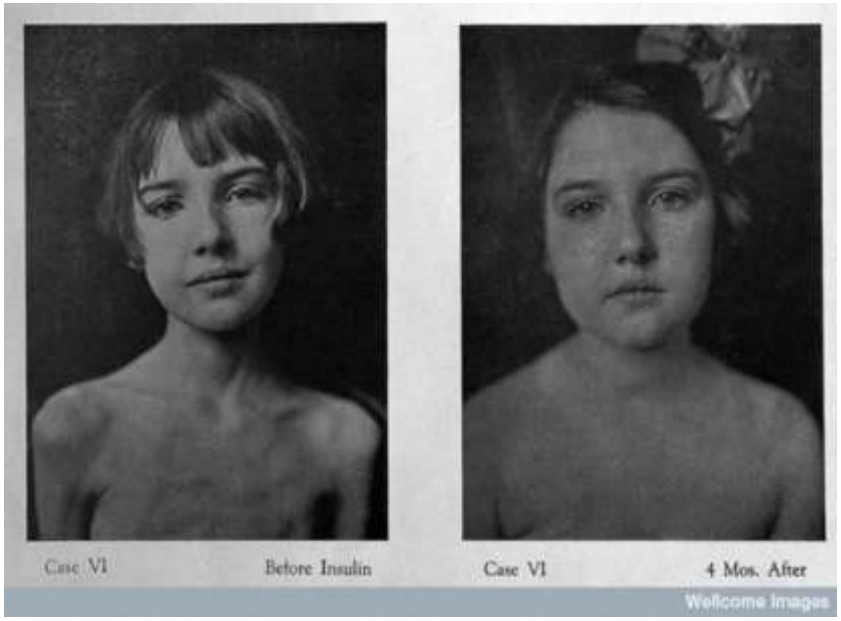
Ghada El-Kanishy

Prof. of Internal Medicine

Mansoura Faculty of Medicine

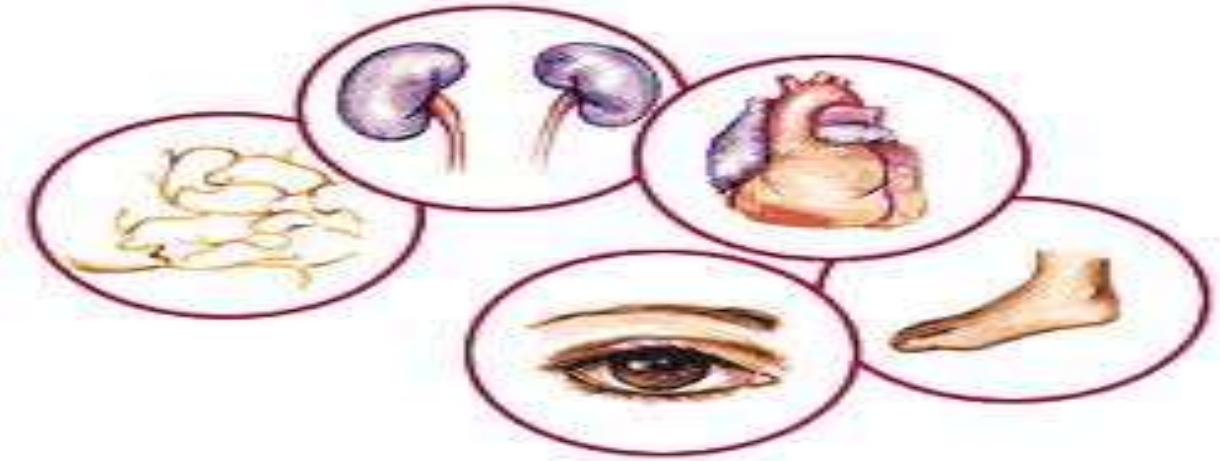
Type I DM

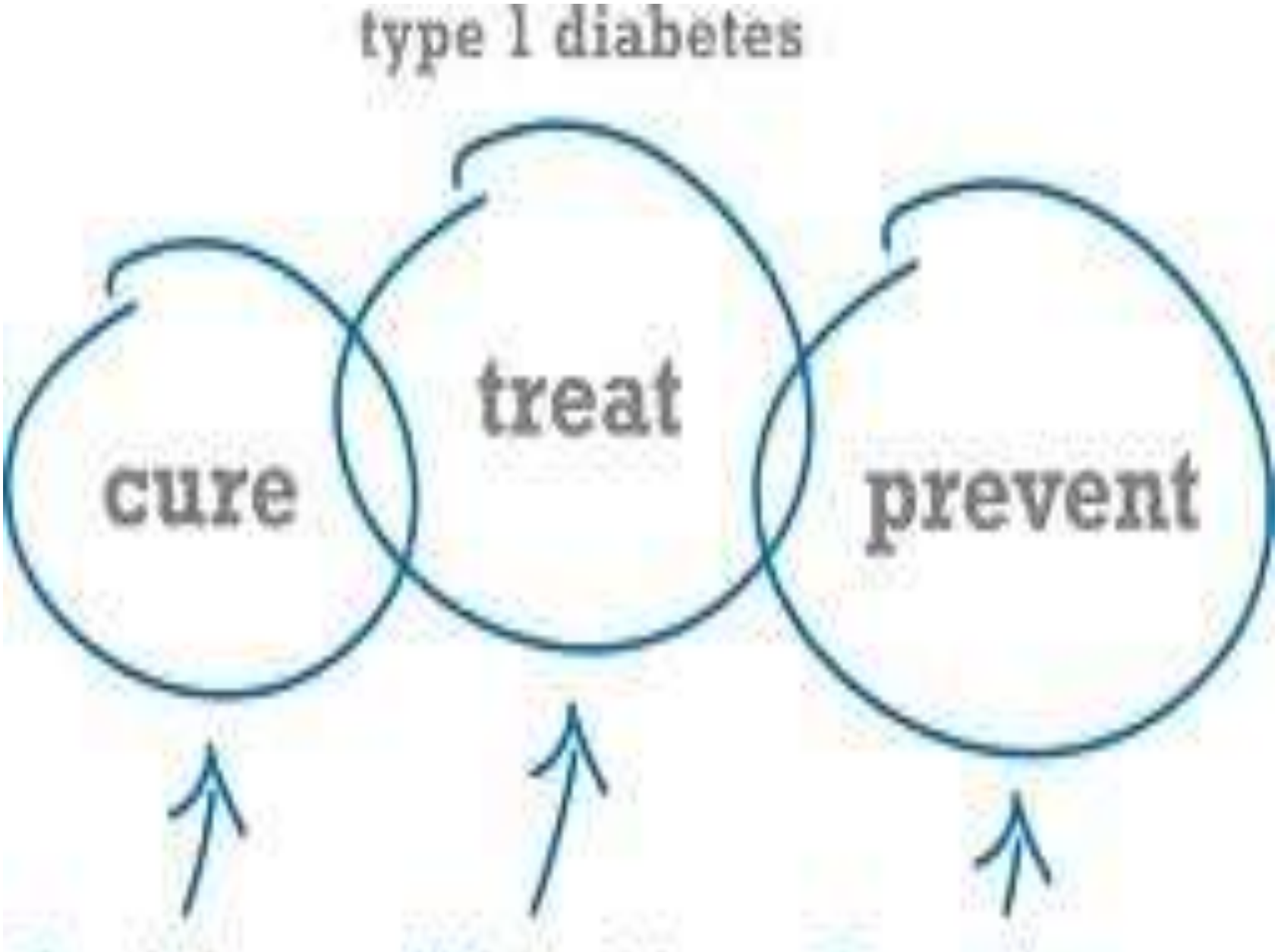



Case VI
Before Insulin
Case VI
4 Mos. After
Wellcome Images

Type 1 diabetes= **Insulin therapy**

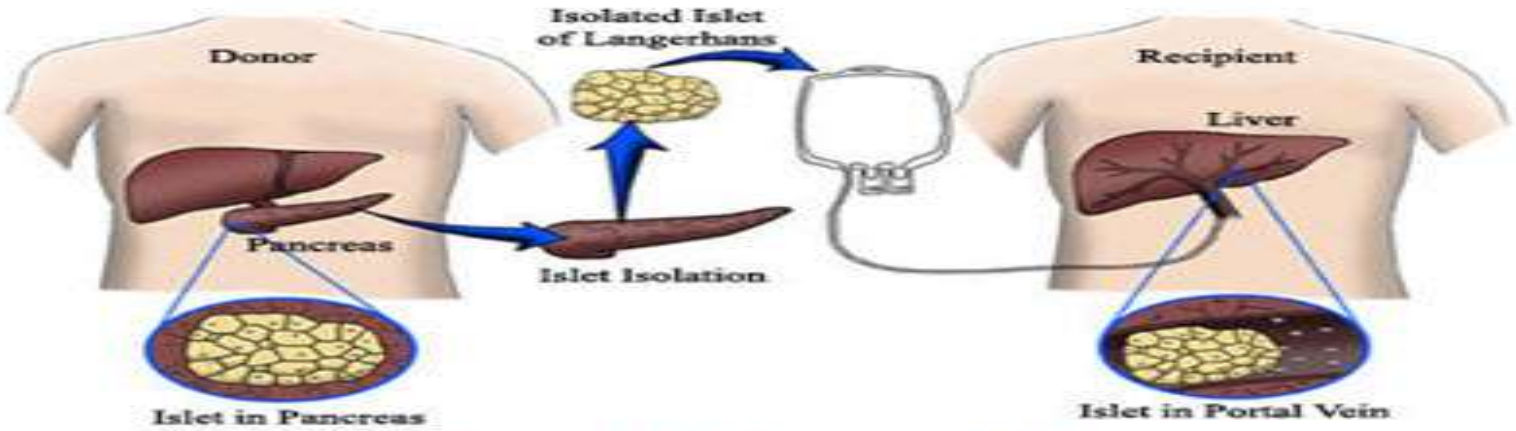
- Despite the success of insulin therapy, it is now obvious that even rigorous control of blood glucose with insulin injections only delays, but does not prevent the development of diabetic complications




type 1 diabetes
cure
treat
prevent

Islet transplantation

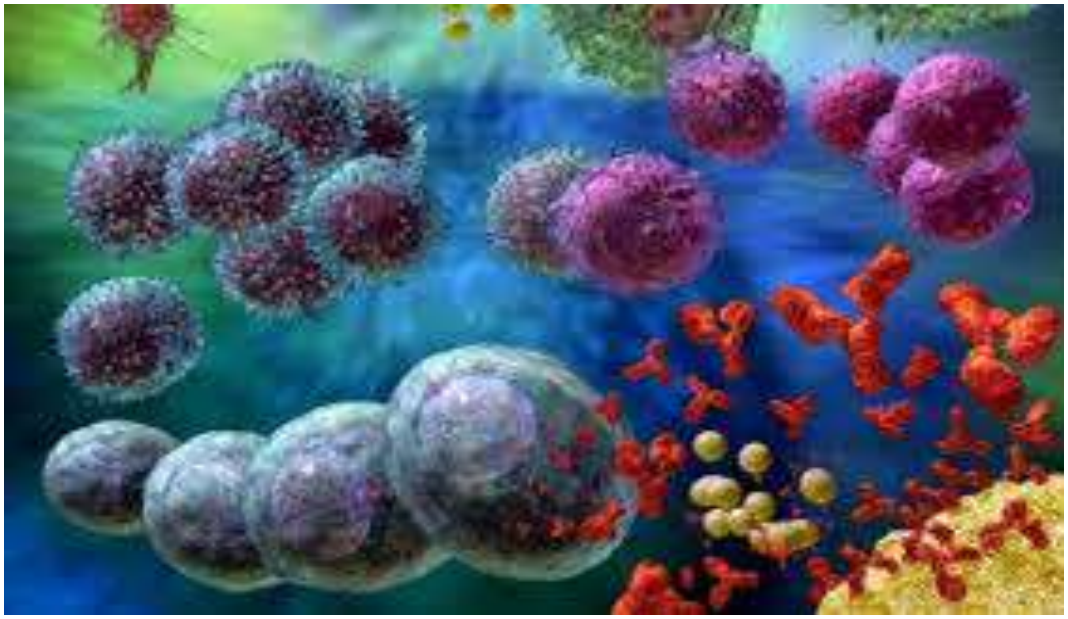
1. sufficient source donors are limiting
2. the possibility of lifelong anti-rejection drugs may prove worse than diabetes
3. the autoimmune process that destroyed the original beta cells are still active




What if you
could help STOP
type 1 diabetes
before it starts?

- Therefore therapeutics that modify the immune response and restore normal immune function are necessary to improve the outcomes of patients with type 1 diabetes.

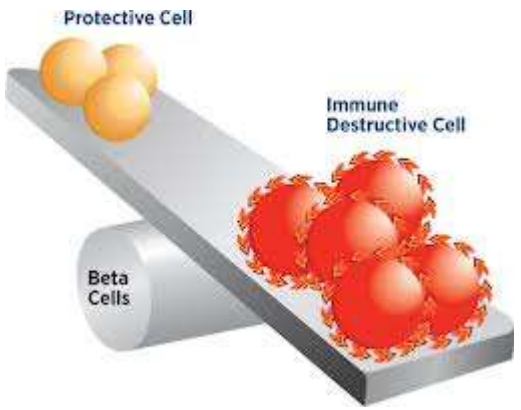
Immunotherapy



Immunotherapy

- Aim:

1. to restore the proper immune system balance preventing further beta cell death.
2. subsiding of beta cell inflammation.
3. increasing insulin production .

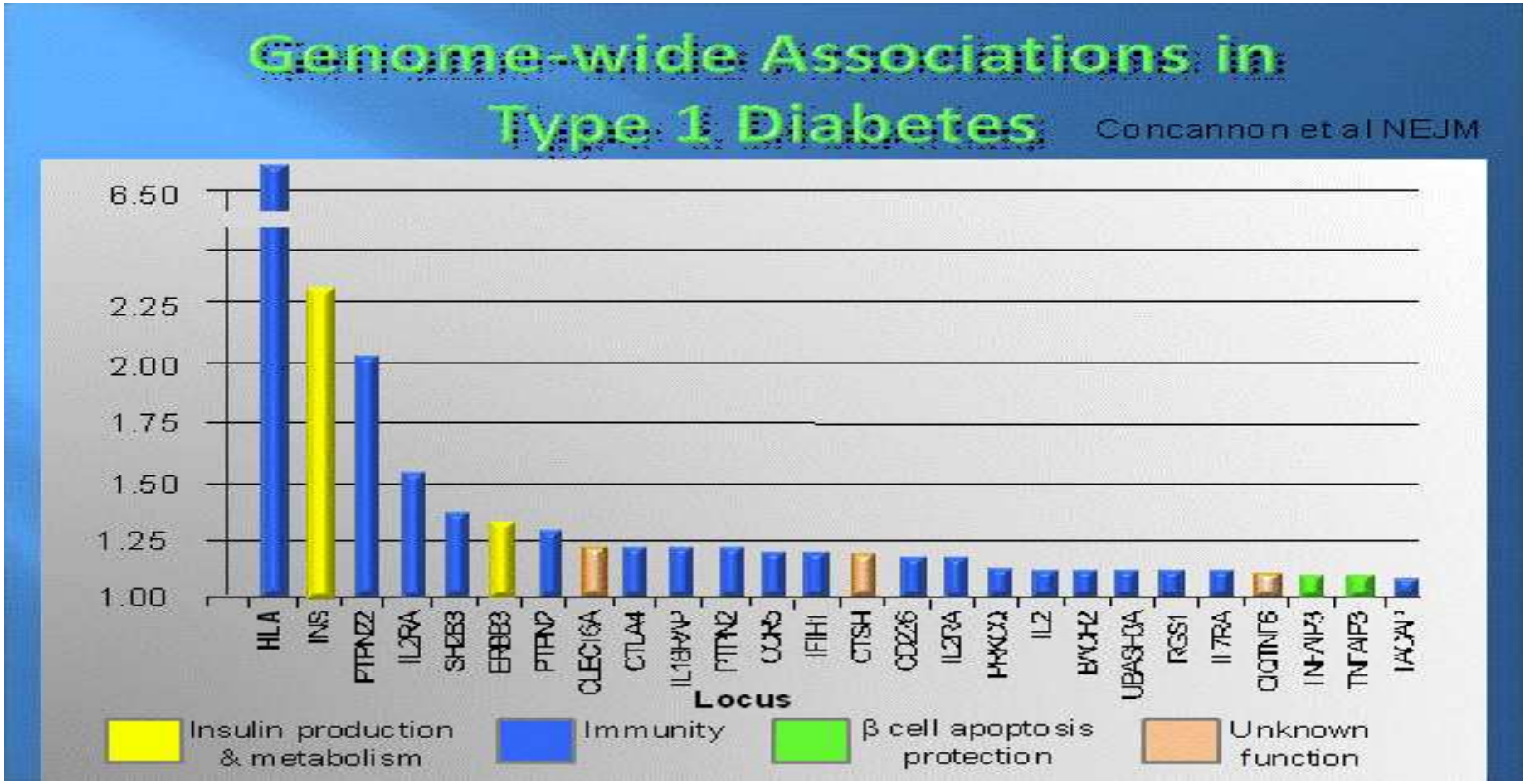


- ✓To effectively accomplish this requires **identification of individuals at risk** of type 1 diabetes.

Prediction of T1D

1) Genetic
2) Immunologic
3) metabolic parameters

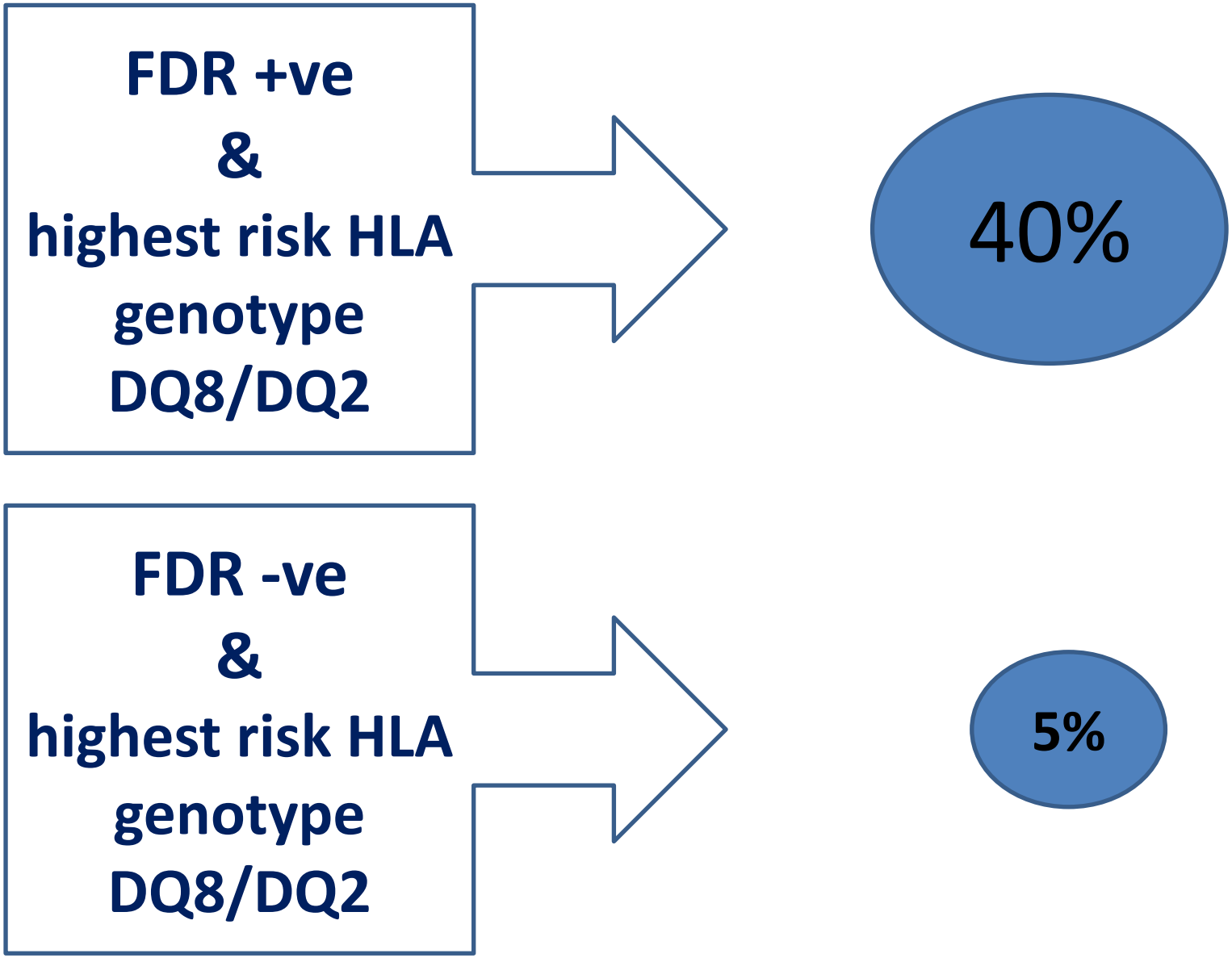
1. GENETIC MARKERS



1. GENETIC MARKERS

- Approximately 50% of the familial aggregation of T1D has been attributed to the HLA region .

- Both DR and DQ alleles have been associated with T1D.


FDR +ve
&
highest risk HLA
genotype
DQ8/DQ2
40%
FDR -ve
&
highest risk HLA
genotype
DQ8/DQ2
5%

2. IMMUNOLOGIC MARKERS

1. ISLET AUTOANTIBODIES:

Several clinically useful serum autoantibodies can be detected during the preclinical period of type 1 diabetes:

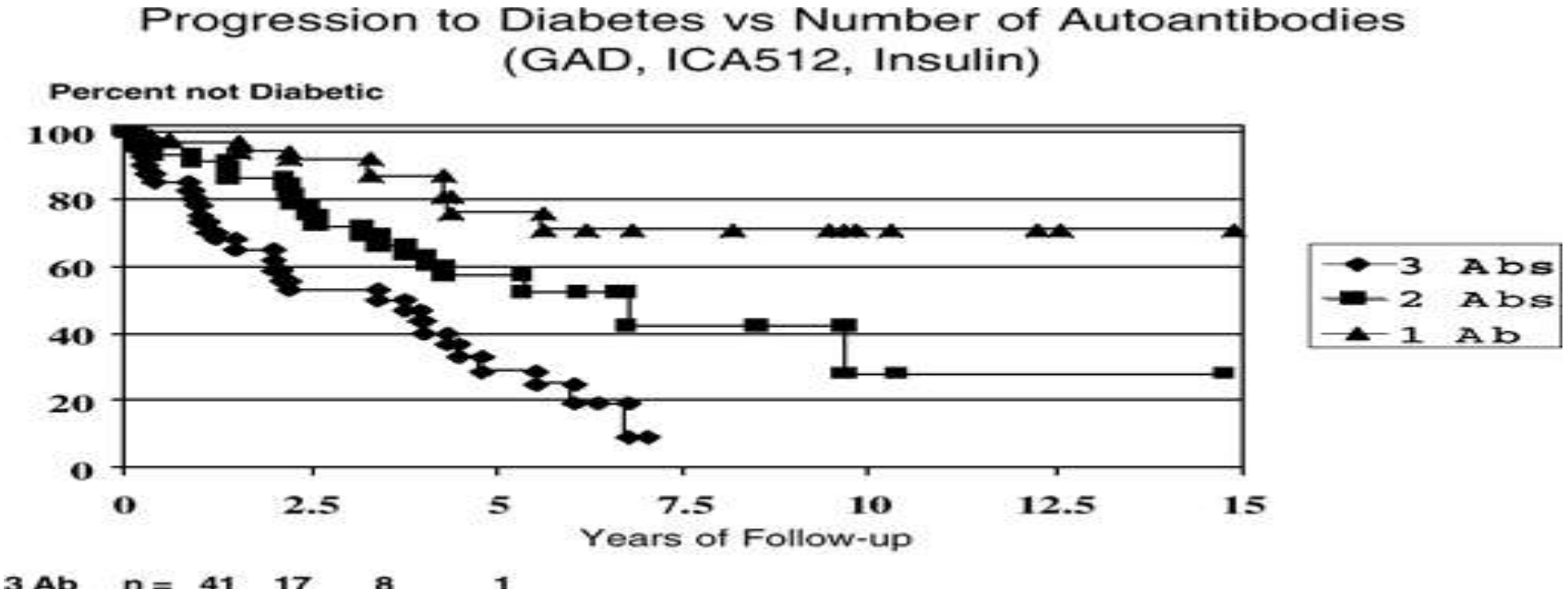
- including islet-cell antibodies (ICA)
- insulin autoantibodies (IAA)
- antibodies to glutamic acid decarboxylase (GAD)
- antibodies to tyrosine phosphatase-like proteins such as insulinoma associated protein (IA-2, ICA512)

2. IMMUNOLOGIC MARKERS

2. ZINC TRANSPORTER ANTIBODIES

- 60 to 80 % of pts with newly diagnosed T1D have ZnT8 autoantibodies.
- The function of this transporter is unknown.

- >one autoantibody had a progressive increase in the prevalence of T1D for up to 15 years, at which point the risk was 66%.
- Approximately 80% of first-degree relatives who express only one autoantibody do not progress to T1D.



3. METABOLIC MARKERS

- The most useful and widely performed test is the acute (or "first phase") insulin response to glucose during an IVGTT.
- In this test the rise in serum insulin above baseline is measured during the first 10 minutes after an intravenous glucose challenge.
- The response correlates with the functioning ß-cell mass.

3. METABOLIC MARKERS

Proinsulin

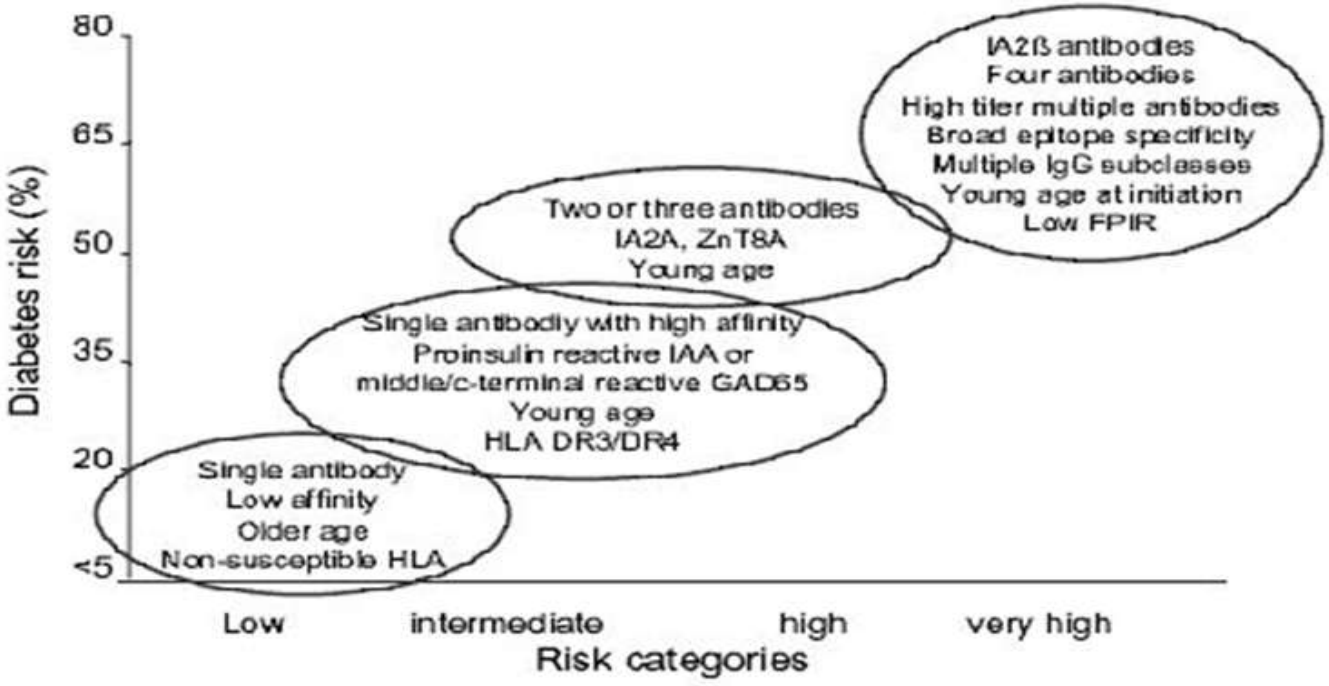
- In normal subjects, proinsulin accounts for approximately 15 %of serum immunoreactive insulin.

- This proportion rises as ß-cell function declines.*(three to four times higher among ICA-positive relatives of T1D patients as compared with ICA-negative relatives).*

- However, prospective studies are needed to determine whether elevated serum proinsulin values will help in predicting the development of T1D.

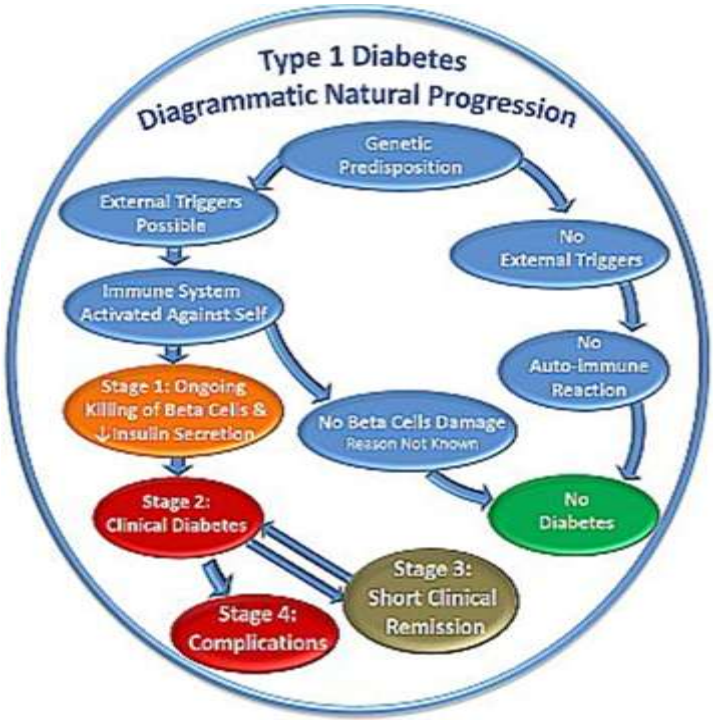
4. COMBINING RISK BIOMARKERS

There is growing evidence that combining multiple genetic and clinical markers is the best way to augment predictive power.

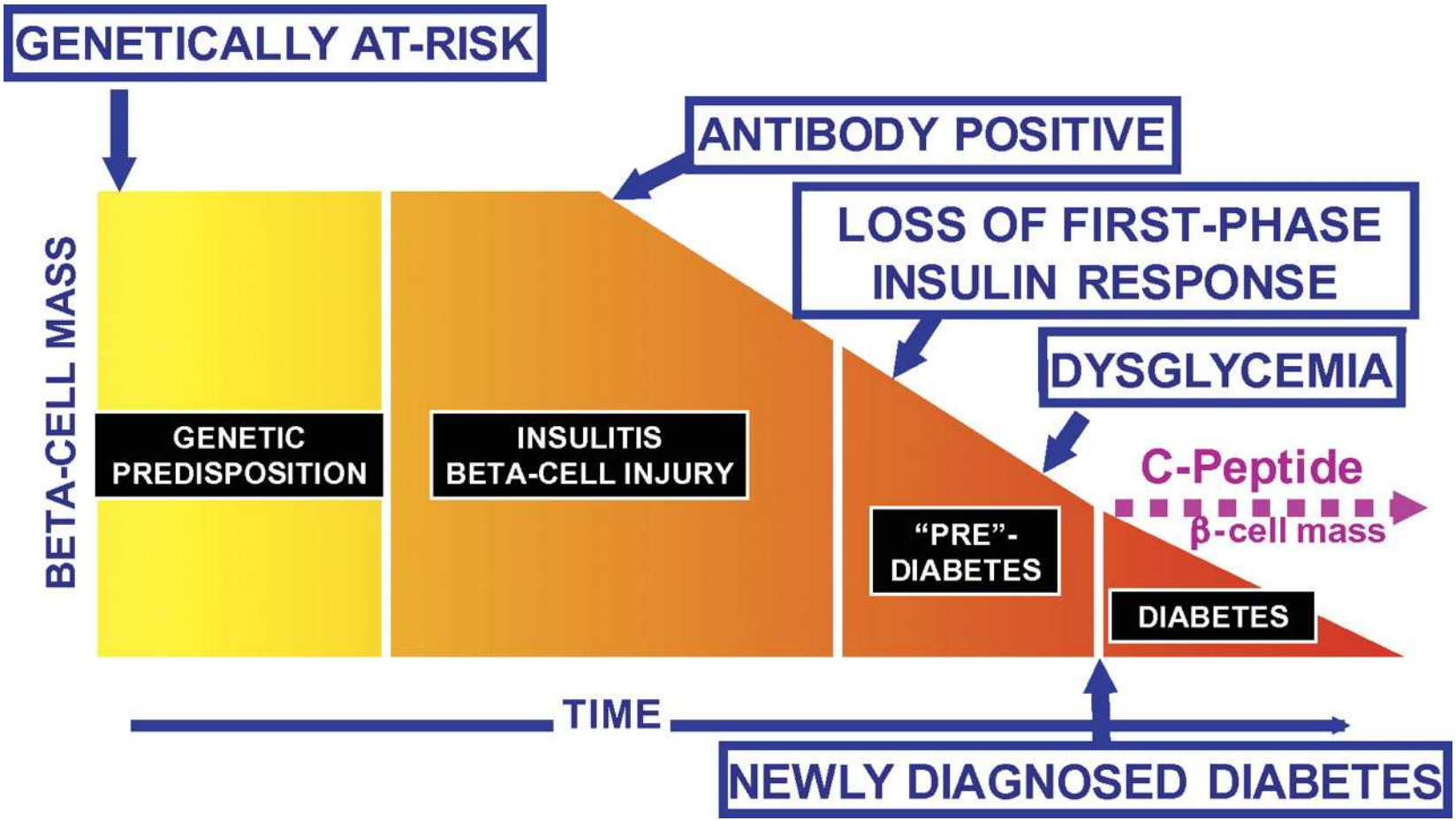


Limitations

- The majority of individuals who present with T1D do not have a known relative who had the disease
- Although these approaches would identify most of those destined to develop type 1 diabetes, but it would also identify a larger number of people who will not develop the disease

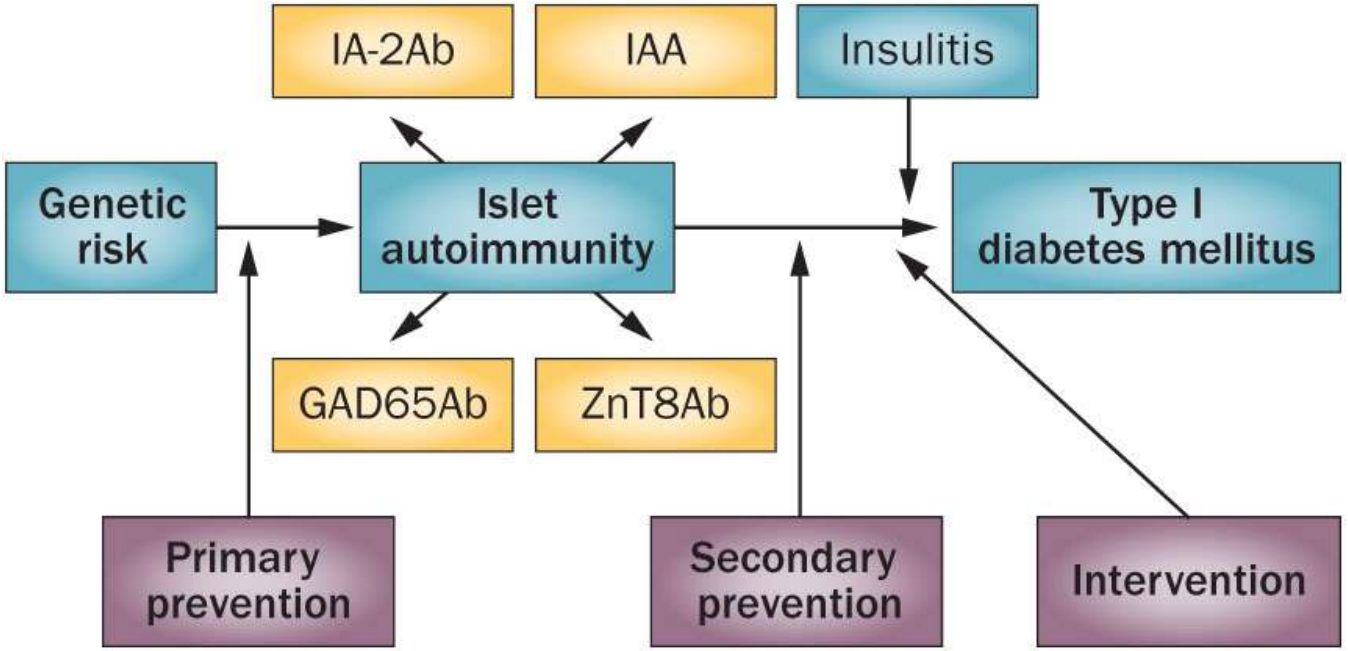


Potential time points for intervention to alter the type 1 diabetes disease process.



Skyler J S , and Ricordi C Diabetes 2011;60:1-8

Figure 1 Representation of type 1 diabetes mellitus aetiology and pathogenesis, which indicates the points at which primary prevention, secondary prevention or intervention can be attempted



Lernmark, Å. & Larsson, H. E. (2013) Immune therapy in type 1 diabetes mellitus
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2012.237

nature REVIEWS ENDOCRINOLOGY

- Studies of immune intervention begun at or shortly after diagnosis of clinical T1D have the advantage that research subjects have an unambiguous diagnosis, but they have the disadvantage that such individuals have fewer β-cells to preserve.

- The goal of such studies is the preservation of residual β-cell function.

Immunotherapy in Type 1 Diabetes

The End of Insulin Treatment?

Immunotherapy

1. Non-antigen-specific immunotherapy
2. Antigen-specific immunotherapy
3. Cell based therapy

NON-ANTIGEN-SPECIFIC IMMUNOTHERAPY

Non-antigen-specific immunotherapy

- ***Cyclosporin A***
  - treatment with CsA had no long-lasting effect on the course of T1D.
  - The need for chronic drug administration, the potential renal and pancreatic β-cell toxicity led to the consensus that the risks outweighed the benefits, and the approach was dropped.

Non-antigen-specific immunotherapy

- ***Mycophenolate mofetil***
  - A combination of MMF and a monoclonal antibody (daclizumab) did not preserve β-cell function in newly diagnosed patients with T1D.

Gottlieb PA et al.*Diabetes Care (2010)*

Non-antigen-specific immunotherapy

- ***Anti-CD20: rituximab***
  - Treatment effect of rituximab was most prevalent **within the first 3 months** of application. Over this time period, the treatment was able to reduce the loss of C-peptide and insulin requirements.
  - Later on, analyses revealed that the effects on C-peptide responses did not prevail.

Pescovitz MD et al. *New Engl J Med (2009).*

Non-antigen-specific immunotherapy

- ***Anti-CD3 therapy: teplizumab and otelizumab***
  - Based on preclinical studies in the NOD mouse setting, two phase II trials were performed and showed a clear effect, with best success seen in patients with higher functional β-cell mass before the start of treatment.
  - Both studies failed to meet their primary end point at 1 year.

Sherry N et al, *Lancet (2011)*

Non-antigen-specific immunotherapy

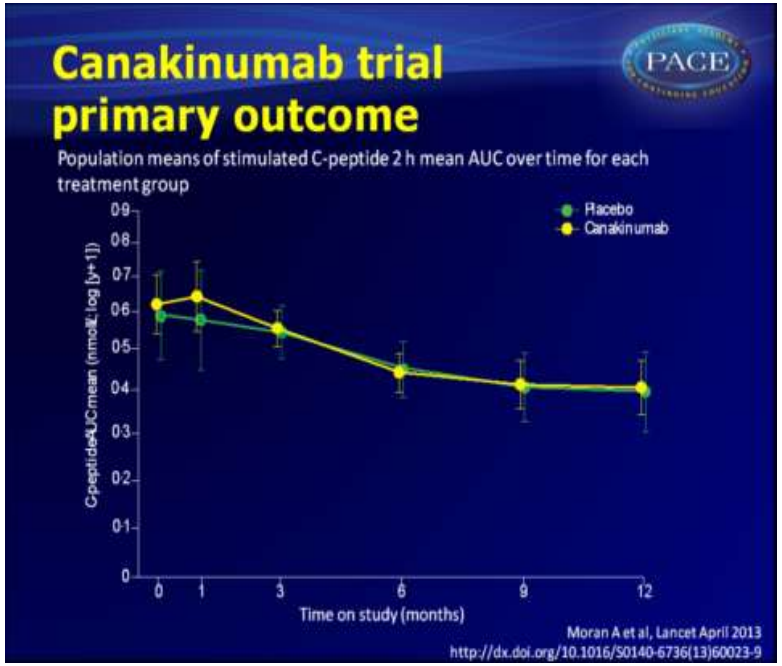
- ***Cytotoxic T-lymphocyte-associated protein 4 immunoglobulin (CTLA4-Ig): abatacept and belatacept***
  - Abatacept treatment resulted in an estimated delay in C-peptide reduction of about **10 months**.
  - A longer follow-up is necessary to determine whether there is a persisting treatment effect maintained after cessation of application.

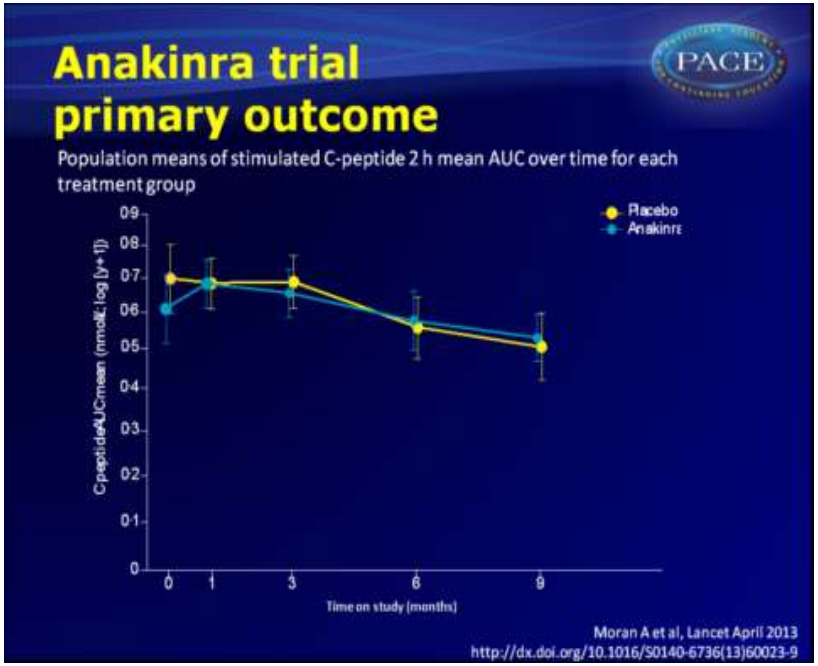
Orban T et al. *Lancet (2011)*

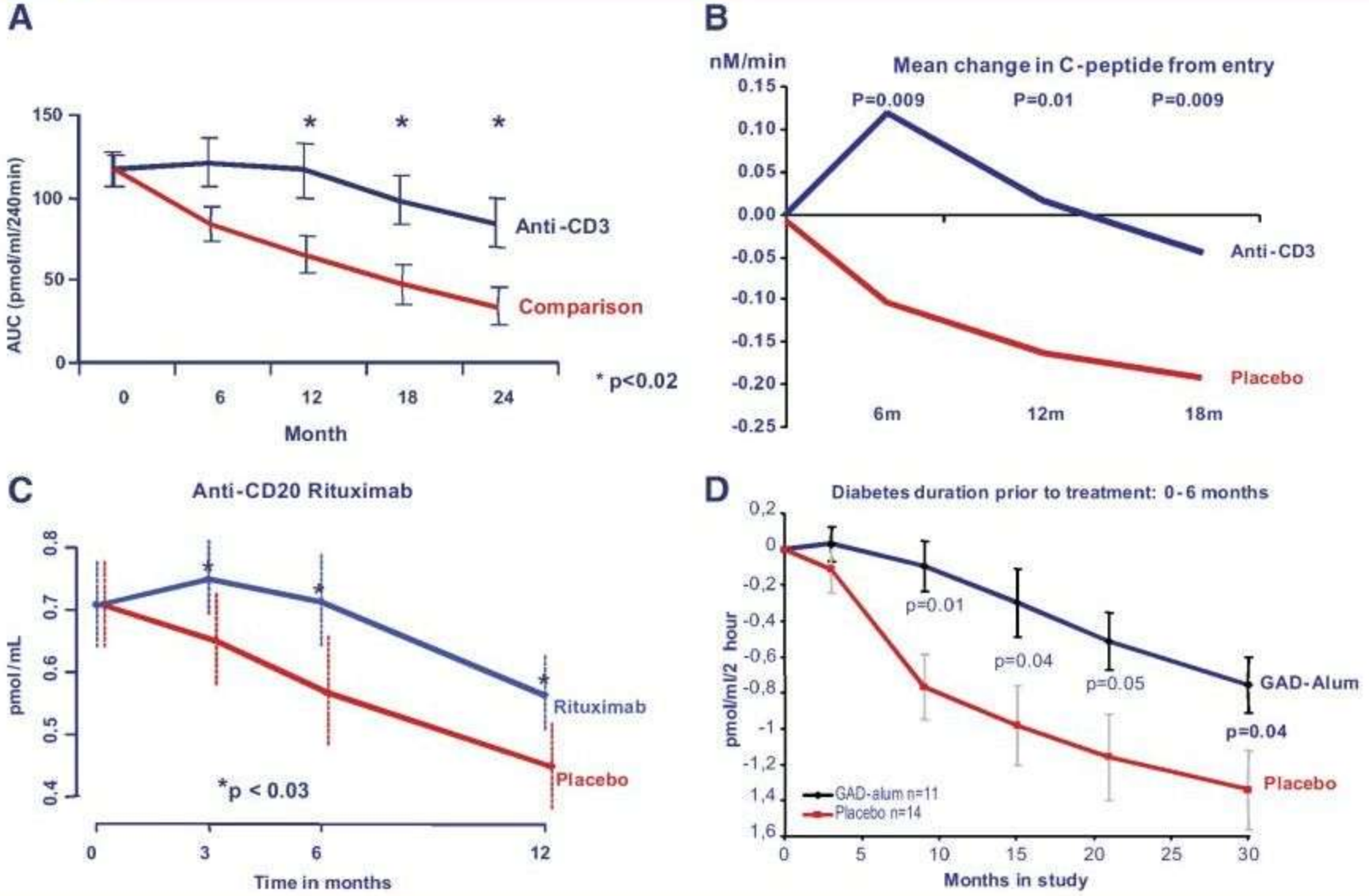
Non-antigen-specific immunotherapy

- ***Anti-interleukin-1 (IL 1) therapy:***

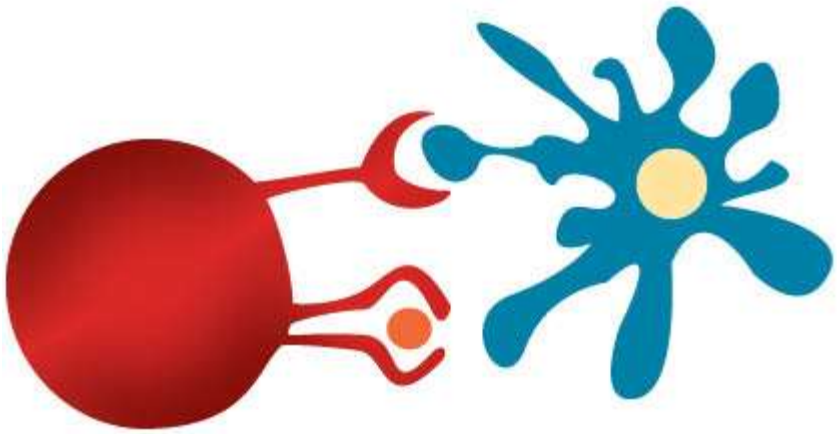
Inhibition of IL-1 with either canakinumab or anakinra did not slow the reduction in β-cell function in new-onset type 1 diabetes.







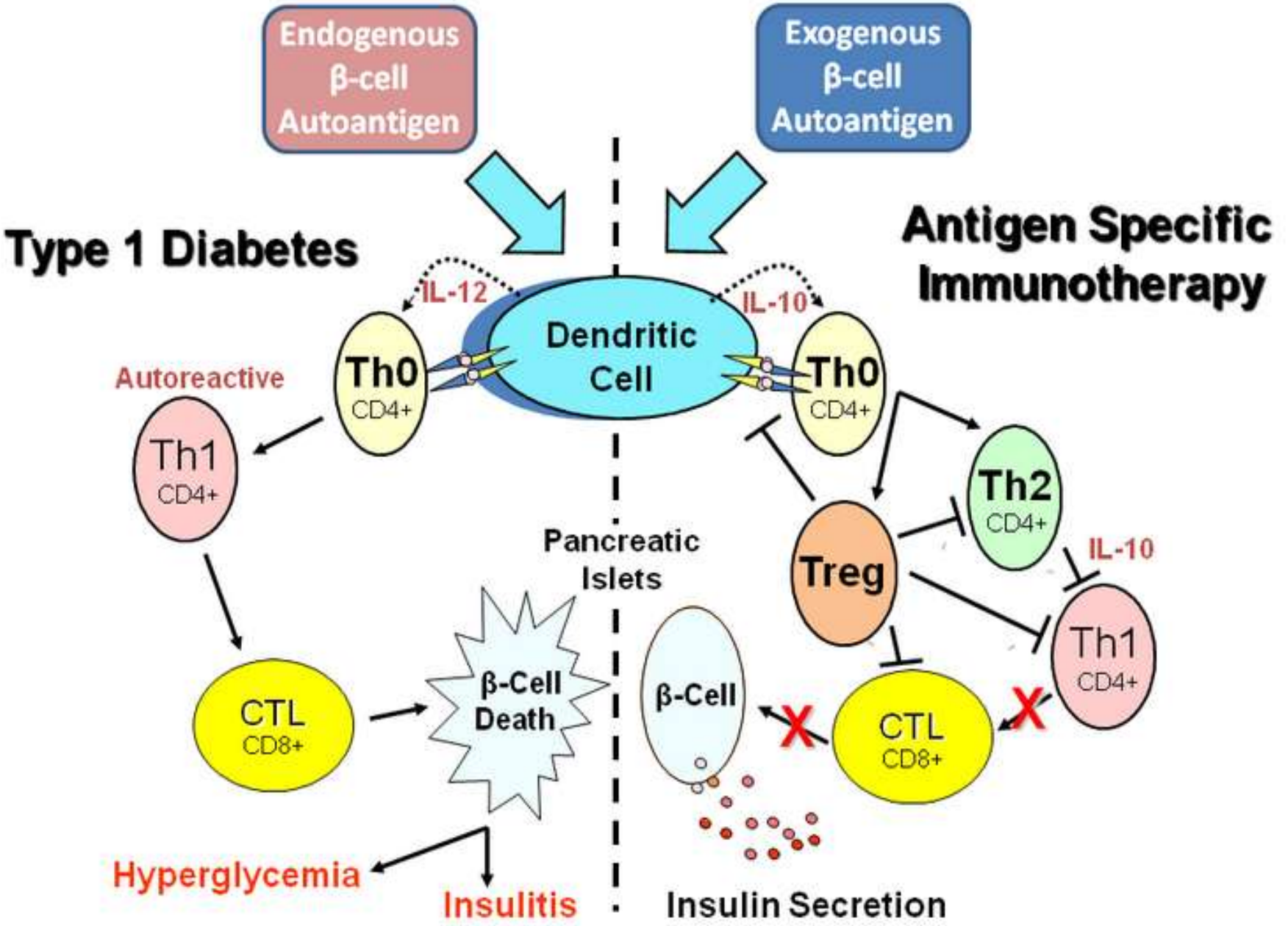
ANTIGEN-SPECIFIC IMMUNOTHERAPY



antigen-specific immunotherapy

Aim: to induce immune tolerance by the use of β-cell autoantigens.

- T-cells are educated in the thymus to learn the difference between “self” and foreign antigens and under normal conditions self reactive T-cells are destroyed. This process breaks down with T1D and other autoimmune diseases resulting in autoreactive T-cells that attacks the host’s body.
- This has lead to the idea that increasing a patient’s exposure to self-antigens may allow the T-cells to be properly educated.


Endogenous β-cell Autoantigen
Exogenous β-cell Autoantigen
Type 1 Diabetes
Antigen Specific Immunotherapy
IL-12
IL-10
Dendritic Cell
Th0 CD4+
Th0 CD4+
Autoreactive
Th1 CD4+
Th2 CD4+
Treg
IL-10
Th1 CD4+
Pancreatic Islets
CTL CD8+
β-Cell Death
β-Cell
CTL CD8+
Hyperglycemia
Insulitis
Insulin Secretion

UTILIZING ISLET AUTOANTIGENS IN IMMUNE THERAPEUTIC TRIALS

Mechanism of action:

- **Immune deviation** associated with change of dominant cellular phenotype (from TH1 to TH2).
- **Immune regulation** may be effective in restoring tolerance.
- **Immune deletion** of B cell antigen specific T cells.

antigen-specific immunotherapy

- what is the best **Time?**

In NOD mice treatment with β-cell autoantigens work with highest efficiency when administered earlier in the course of the disease, long before the onset of hyperglycemia.

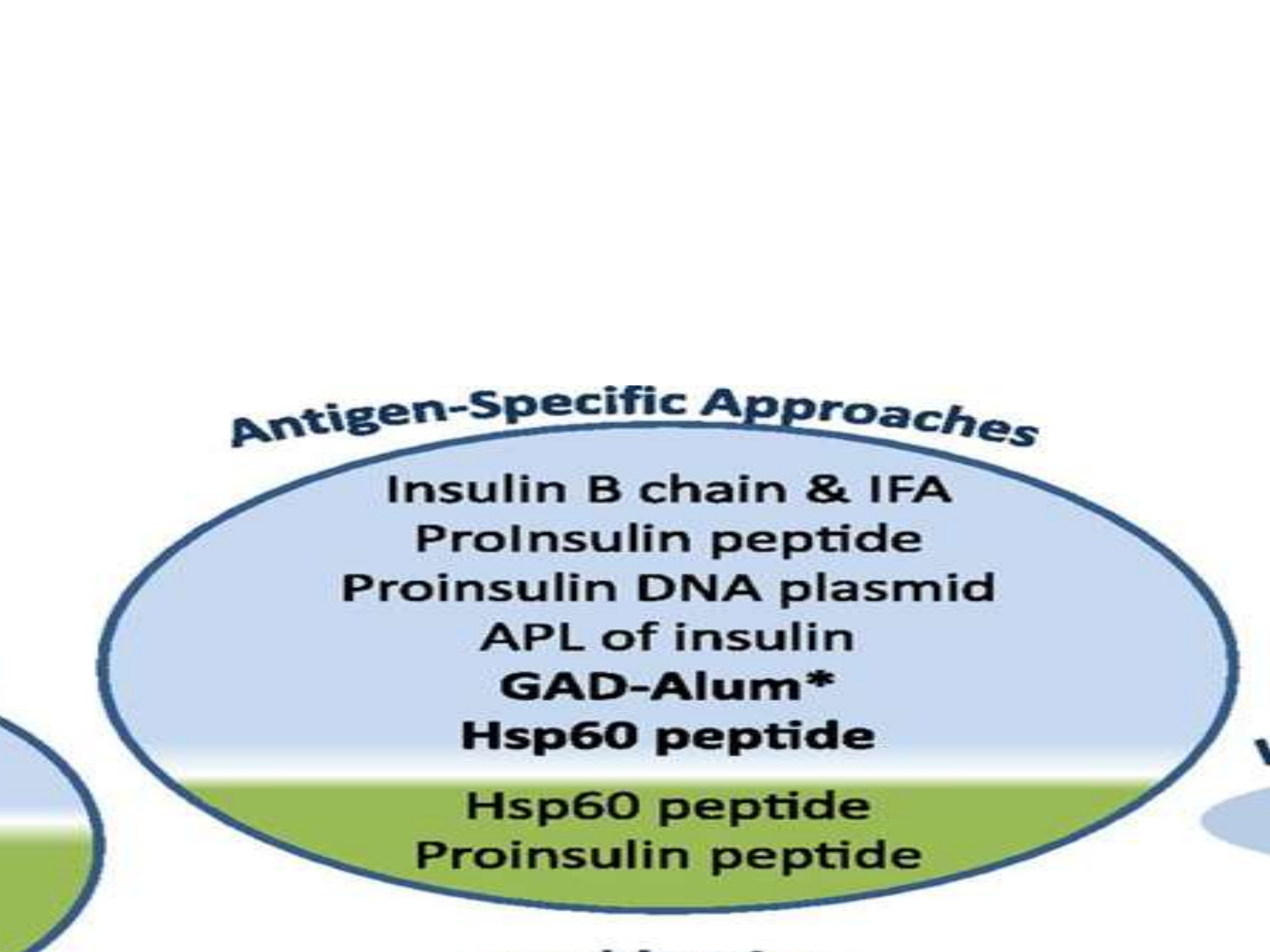
antigen-specific immunotherapy

- what is the best autoantigen to use?

Autoantigen	distribution	Mice		Men		Comments
		AutoAbs	T cells	AutoAbs	T cells	
Preproinsulin	β cells, thymus	Yes	CD4	Yes	CD4, D8, aTregs	AAb affinity matters; CD8 T cells lyse β cells in a glucose-dependent manner; genetically determined variation in gene expression in β cells vs. thymus
Glutamic decarboxylase 65 (GAD65)	Islet cells, adrenal gland, CNS, neurons, testis, ovary	No	CD4	Yes	CD4, CD8	Not expressed in mouse β cells; AAb associated with HLA-DR3-DQ2
GAD67	Islet cells, neurons	No	CD4	Yes	CD4	Not expressed in human β cells

Tyrosine phosphatase like autoantigen or insulinoma antigen-2 (IA-2; ICA512, PTPRN)	Islets	Yes	CD4	Yes	CD4, CD8	AAb associated with DR4-DQ8; alternative splice variation; truncated variant: ICA512
IA-2β (Phogrin, PTPRN2)	Islets	No	CD4	Yes	CD4	
Islet cell antigen-69 (ICA69)	Pancreas, heart, and brain	No	No	Yes	CD4	Inverse correlation between AAb and T-cell responses; AAb associated with HLA-DR4, T-cell responses with -DR3
Zinc transporter-8 (ZnT8)	β cells					Polymorphic
Chromogranin A	Neuroendocrine cells	No	CD4	No	?	
Ganglioside	Ubiquitous	No	No	Yes		

38 kDa granule antigen	Neuroendocrine cells	No	?	Yes	Yes	
Peripherin	Neurons	No	CD4	?	?	No evidence of differential recognition in human type 1 diabetes
Islet amyloid polypeptide (ppIAPP)	Islets	No	CD4	No	CD8	Immune responses not specific for diabetes
Carboxypeptidase H/E	Neuroendocrine cells; adrenals	No	No	Yes	No	
Heat shock protein 60 (hsp60)	Ubiquitous (mitochondria)	No	CD4	No	CD4	Immune responses not disease specific
IGRP;						


Antigen-Specific Approaches
Insulin B chain & IFA
ProInsulin peptide
Proinsulin DNA plasmid
APL of insulin
GAD-Alum*
Hsp60 peptide
Hsp60 peptide
Proinsulin peptide

Risk analysis for antigen-specific immunotherapy

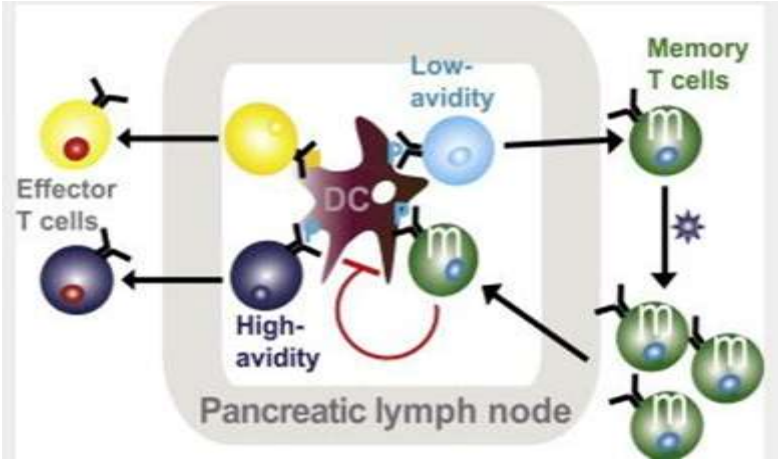
1. acceleration of disease, leading to more rapid β-cell loss.
2. induction of life-threatening hypersensitivity.
3. induction of “off-target” autoimmunity.

Risk analysis for antigen-specific immunotherapy

- Additional challenges, however, remain, including

1. the wide heterogeneity of T1D
2. the limitation of lymphocyte analysis from peripheral blood
3. Autoantigen choice, dose and frequency of administration.

CELL BASED THERAPEUTICS

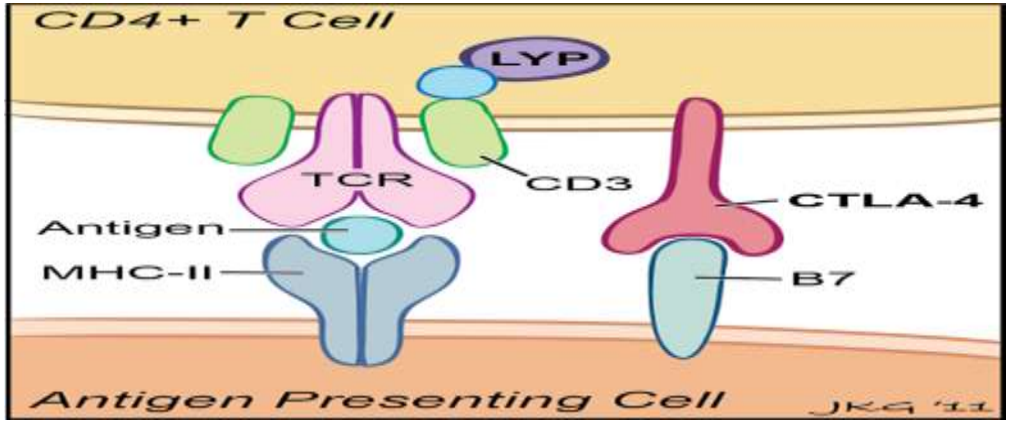


Cell based therapeutics

- Cell based therapeutics use natural or modified immune cells transplanted into a host.
- The majority of cell-based has focused on DC's, the regulators of the immune system.

Cell based therapeutics

- Under normal conditions the DC migrate through the body sampling the environment around them.
- DC then present the self-antigens to naïve T-cells promoting and maintaining self-tolerance.

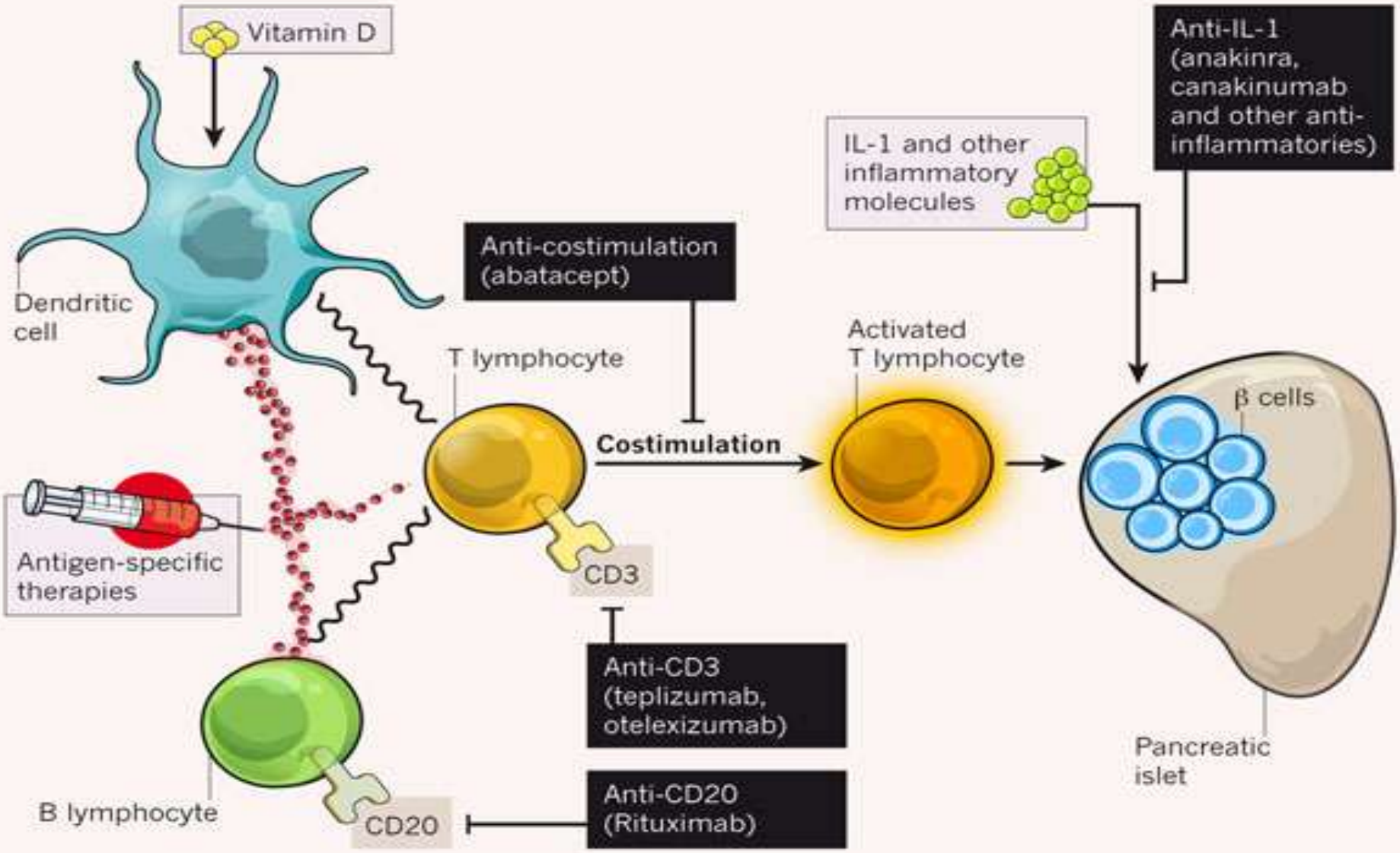


Cell based therapeutics

- This aspect of DC makes it an ideal target for autoimmune disease therapy in order to maintain auto-reactive T-cell populations silent or hyporesponsive.
- Method is based on harvesting DC's from the mouse and then modifying before being reintroduced back into the mouse.
- Stabilization of DC in an immature state promote T-cell hyporesponsiveness and an overall state of tolerance

IMMUNOTHERAPY

The object in each case is to prevent the immune system (T cells) from attacking the beta cells in the pancreatic islet (shown on the right).



Conclusions

Some approaches have shown promise in recent-onset type 1 diabetes:

- anti-CD3 monoclonal antibodies (teplizumab and otelixizumab)
- anti-CD20 monoclonal antibody rituximab
- GAD vaccine

Conclusions

- Although considerable work remains to be accomplished, the potential to prevent T1D is clearly within reach.

- Approaches that are more aggressive than those used in the past, including combination approaches and novel interventions, will likely be needed.


THANK
YOU!
March of Dimes